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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,096	03/11/2004	Rea-Min Chu	P/741-176	6503

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/798,096	CHU ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 16* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group I, claims 1-14 and 16, drawn to a complex immuno-gene medical composition for inhibiting tumor cells, comprising DNA Sequences SEQ ID NO 1 and SEQ ID NO 2, and a method of using the composition to inhibit the growth of tumor cells, and CTVT as the species of tumor cells and muscle electroporation as the species of plasmid administration, in the reply filed on 7/28/2005 is acknowledged.

Claim 15 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/28/2005.

Claims 1-14 and 16 are currently under consideration.

Specification

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms, which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: CTVT "is naturally occurred, poorly differential tumor cells" (pg. 1, pgph 2); "CTVT are lymphocytes being non-T or non-B cells, which are not able to express antigens characterized as T-cells and B- cells (pg 1, pgph 3); and "For evidencing the effect of the combined usage of IL-6 and IL-15 plasmids, the constructed IL-6 and IL-15 plasmids are muscle electropolated" (pg. 11, pgph 36). Numerous other grammatical and/or spelling errors are found throughout the specification. The

specification uses grammar and phrasing so tortured, and without any regard to the usage of proper verb tense, as to make the disclosure nearly incomprehensible for the purposes of examination. Applicant is required to provide a fully corrected specification, without introducing new matter.

Claim Objections

Claims 1-14 and 16 are objected to because of the following informalities: The claims contain multiple grammatical errors and misspellings. For example claim 1, line 1 says "which medical composition", it is suggested that applicant intended to use "said" instead of "which". Additionally, it is noted that DNA sequences do not express, they encode proteins (see claims 1,7 and 16). Further, claim 4, line 1, is drawn to PGF-β. In view of the specification, the other claims, and the utter lack of support in the art for the term PGF-β it is suggested that applicant meant to use the term TGF-β. The claims frequently lack modifiers, such as "the" (claim 4, line 2) or use the wrong modifier such as "to" instead of "in" or "the" (claim 7, line 5). Finally, the claims use parenthesis to set off the SEQ ID: Nos, this is improper since it is impossible to tell if applicant means to specifically claim the SEQ ID NO, or to merely indicate it as representative of a possible sequence. Numerous other errors abound. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a therapeutic composition for inhibiting Canine transmissible venereal tumor (CTVT) cells, comprising a plasmid comprising SEQ ID NO:1 encoding IL-6 and a plasmid comprising SEQ ID NO:4 comprising an IL-2 signal peptide operably linked to IL-15, and a method of inhibiting the growth of CTVT tumor cells in CB-17 SCID mice, *in situ*, by administering the plasmids via muscle electroporation, does not reasonably provide enablement for a therapeutic composition for inhibiting any tumor cells, comprising a plasmid comprising SEQ ID NO:1 encoding IL-6 and a plasmid comprising SEQ ID NO:2 encoding IL-15, and a method of inhibiting the growth of any tumor cells in CB-17 SCID mice, *in situ*, by administering the plasmids via muscle electroporation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a composition for gene therapy, comprising a plasmid comprising SEQ ID NO:1, encoding IL-6 and a plasmid encoding SEQ ID NO:2, encoding IL-15, used for treating tumor cells such as CTVT, wherein the composition may antagonize PGF-β (presumed TGF-β) and activate NK cells to inhibit the growth of tumor cells, and a method for gene therapy, comprising inhibiting tumor cell growth, such as CTVT with said composition.

The specification provides guidance on the manufacture of two plasmids: one comprising a sequence encoding human IL-6 (SEQ ID NO:1); and the second comprising a sequence encoding the human IL-2 signal peptide (IL-2SP operably linked to a

sequence encoding the mature human IL-15 peptide, which forms a chimeric IL-2 SP/IL-15 gene (SEQ ID NO:4) (Specification, pg. 13, pgph 40). No other plasmids are disclosed. Further the specification teaches that when the plasmids are electroporated into CB-17 mice, seven days after the mice were injected with xenogeneic CTVT tumors, the tumors showed a decrease in tumor size at day 14 in comparison to mock controls. Based on these *in vivo* results applicant's claim their instant invention.

Canine transmissible venereal tumor or CTVT cells are round neoplasms that primarily infect dogs and {Hsiao et al. (2002) Veterinary Immunology and Immunopathology 87:19-27; pg 19, col. 2}. CTVT cells initially do not express MHC class I and II molecules during P phase, however CTVT cells dramatically increase expression of MHC class I and II molecules during R phase, which leads to a reduction of tumor growth as the host's anti-tumor immune response is triggered (Abstract, pg. 20, col. 1, pgph 1). Hsiao et al. teaches that tumor infiltrating lymphocytes (TIL) secrete a substance that triggers over-expression of MHC molecules in CTVT cells. It is noted that the working examples in the specification do not indicate what the average phase of the CTVT cells transplanted into the mice were, or if there was MHC I or II expression by the CTVT cells used. Further mouse NK cells express a variety of activation receptors that recognize MHC class I molecules, such as the LY49 receptors {Silver et al. (2000) J. of Immunology. 165:1771-1781; pg. 1771, col. 1}.

The basic premise of the claimed invention is that the NK cells have been upregulated in the SCID mouse model, by increased expression of IL-6 and IL-15 after administration of the claimed plasmids. However, the working examples do not analyze or indicate what effect these cytokines have on the CTVT cells. Specifically, whether or

not the CTVT cells showed increased expression of activation ligands for mouse NK cells and/or decrease of TGF-β release or decreased expression of any mouse NK inhibitory ligands. There is no information described in the specification on the expression of NKG2D ligands on the CTVT cells. Mouse and human NKG2D activation receptors bind to non MHC class I or II ligands, such as MICA, MICB, ULBP, Rae1 and H60, amongst others {Raulet et al. (2003) Nature Reviews Imm. 3:781:790; pg. 782, Figure 1; pg. 784, Figure 4}. These receptors have distinct patterns of expression, and many of them are associated with tumorgenic or virally infected cells. Further, NK cells express inhibitory receptors, such as ILT-2, which recognize non-MHC ligands such as UL18 {Borrego et al. (2001) Mol. Immunol. 38:637-660}. Given the xenogeneic nature of the interactions between the SCID mouse NK cells and the CTVT tissue, and the limited knowledge in the art on the ligand expression of CTVT cells and their ability to interact with mouse immune cells, it is difficult to assess the nature of the binding interactions between the host immune cells and the xenogeneic tumor cells. Further, the host CB-17 SCID mice lack function al B and T cells due to defective V(D)J recombination, yet they express functional myeloid cells, such as macrophages, in addition to NK cells. Macrophages are known to target CTVT cells during tumor regression {Perez et al. (1998) Vet. Immun. and Immunopath. 64:133-147; Abstract}. Macrophages are known in the art to be activated by IL-15.

The disclosed invention could be mediated by at least two different host cell types, macrophages or NK cells, acting independently or in concert with each other. This question is not answered by the specification, which indicates that the TILs infiltrating the CTVT tumors in the model are presumed to be NK cells based solely on a lack of

expression of T and B cell antigens (Specification pg. 2, pgph 3) The decrease in CTVT size which is considered indicative of the therapeutic ant-tumor attributes of the claimed invention and the method of using could reasonably be due to changes in the expression of various surface ligands/antigens on the surface of the CTVT cells, such as increased expression of MHC I ligands (previously reported to occur during R phase; see Hsiao et al.) , decreased expression of inhibitory ligands, increased expression of non-MHC activation ligands, or any combination thereof. In other words the anti-tumor growth response caused by the claimed composition is reasonably likely to be due to the effects of the cytokines on the CTVT cells rather than any effector cells. This possibility is not answered by experiment described in paragraph 57, since the antibody merely partially blocks NK cell function, but does not answer the question of whether the claimed composition is inducing a response in the CTVT cells or effector cells. Given the paucity of information disclosed in the specification on the specific NK immune response which decreased the tumor size as a result, the xenogeneic nature of the model system, the unknown expression of immune cell activating and/or inhibitory ligands by CTVT cells, and the difficulty in correlating results from the exogenous xenogeneic/ SCID tumor models to endogenous tumors in immunocompetent animals the skilled practitioner would not predict that the claimed composition or method of use could be predictably used to reduce the size of any other tumor in any other species, other than CTVT cells in CB-17 SCID mice without extensive and undue experimentation.

Further, the claims encompass a method of gene therapy using any plasmids separately encoding SEQ ID NO:1 and SEQ ID NO:2, comprised within any vector and administered by any means, such as viral administration. In the past the Achilles heel of

gene therapy has been gene delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, col. 3, pgph 2}. The difficulties in getting genes transferred efficiently to target cells and getting them expressed remained a problem at the time of filing. Pfeifer and Verma state that even "though gene therapy holds great promise for the achievement of this task, the transfer of genetic material into higher organisms still remains an enormous technical challenge {Pfeifer and Verma (2001) Annu. Rev. Genomics. Hum. Genet. 2:177-211; pg. 177, pgph 1}. Johnson-Saliba et al. concurs stating that "although thousands of patients have been involved in clinical trials for gene therapy, using hundreds of different protocols, true success has been limited. A major limitation of gene therapy approaches, especially when non-viral vectors are used, is the poor efficiency of DNA delivery." {Johnson-Saliba et al. (2001) Curr. Drug. Targets 2:371-99; Abstract}. Such problems with delivery continue to plague the field of gene therapy. Shoji et al. has characterized the current state of the art as the "tragic failure of gene therapy" because of poor delivery of gene based-medicines due to the lack of an appropriate vector that "fulfills the necessary requirements, including high transfection efficiency, non-toxicity, non-pathogenicty, non-immungenicty, [and] non-tumorgenicity." {Shoji et al. (2004) Current Pharmaceutical Design 10 :785-796}. The long-standing problems in the field of gene therapy indicate that the results observed by the applicants, in CB-17 SCID mice via muscle electroporation with plasmid DNA, are not sufficient to allow a practitioner skilled in the art to predict how to successfully practice the claimed invention *in vivo* with any vector, by any means of administration in order to inhibit tumor cell growth.

Given the lack of guidance in the specification on the administration of the claimed composition using any other method than muscle electroporation the skilled practitioner would not be able to predict how to practice the claimed invention, except as, a therapeutic composition for inhibiting Canine transmissible venereal tumor (CTVT) cells, comprising a plasmid comprising SEQ ID NO:1 encoding IL-6 and a plasmid comprising SEQ ID NO:4 comprising an IL-2 signal peptide operably linked to IL-15, and a method of inhibiting the growth of CTVT tumor cells in CB-17 SCID mice, *in situ*, by administering the plasmids via muscle electroporation, without undue and extensive experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is so badly mangled as to be completely incomprehensible. Claim 4 refers to PGF-β, a term that is unknown in the art, but as previously noted is presumed to be a typo and should read on TGF-β. Further claim 4 reads on "wherein the composition antagonizes PGF-β [TGF-β] inhibit NK cells with IL-6 and activates NK cells to enhance immune system with IL-15 in host body to inhibit growth of tumor cells. First, the fractured phrasing makes the claim read on inhibiting NK cells with IL-6. This reading of the claim is not supported in the specification or the remaining claims. Second applicant's use of the terms "IL-6" and "IL-15" in the context of the claim make it unclear if IL-6 and IL-15 are separately administered proteins rather than products of the plasmids found

in the composition. It is impossible to discern the metes and bounds of this claim.

Appropriate correction is required.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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